



**INTERNATIONAL CONFERENCE ON HARMONISATION
OF TECHNICAL REQUIREMENTS FOR REGISTRATION
OF PHARMACEUTICALS FOR HUMAN USE**

**eCTD IWG Question and Answer
and Specification Change Request Document**

**Version 1.8
November 18, 2004**

Document Change History

Version Number	Date	Description
Version 1.0	January 2003	Initial Baseline after reviewing questions submitted to ICH
Version 1.1	February 2003	ICH Steering Committee Meeting in Tokyo
Version 1.2	July 2003	ICH Steering Committee Meeting in Brussels
Version 1.3	July 2003	ICH Steering Committee Meeting in Brussels FDA Lawyer Comments
Version 1.4	July 2003	Following ICH Steering Committee Meeting in Brussels
Version 1.5	November 2003	ICH Steering Committee Meeting in Osaka
Version 1.6	January 2004	Following IFPMA notification of formatting problems
Version 1.7	June 2004	ICH Steering Committee Meeting in Washington
Version 1.8	November 2004	ICH Steering Committee Meeting in Yokohama
Version 1.9	May 2005	ICH Steering Committee Meeting in Brussels

Introduction

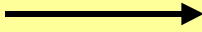
This question and answer document is a summary of questions reviewed by the eCTD Implementation Working Group (IWG) on the eCTD Specification. The questions answered here relate to common questions that relate to the eCTD in all three ICH regions. Many of the questions received on the Step 2 specification were addressed in Step 4 and do not appear in the list. Questions concerning the timeframe for implementation of region-specific application types, module 1 implementation, lifecycle management and those questions that relate to items in the specification that direct the reader to each region are answered in guidance documents published for each region.

Questions related to the table of contents for the Common Technical Document (CTD) should be directed to the CTD question and answer section of the ICH Website.

Some of the questions posed so far address change requests to the eCTD Specification. The change request section of this document addresses all those items received by the eCTD IWG and indicates their status.

This document will be updated as the specification undergoes change control or as new questions are submitted to the eCTD IWG.

No.	Question	Answer	Approval Date
1	A paper CTD may contain more than one copy of the same document. In the eCTD, do you have to include more than one copy of a file?	Separate entries in the XML backbone for each reference of the file can accommodate this need. The file should be included once in an appropriate place in the folder structure. Avoid duplicating the file.	February 2003
2	How should cross-references be presented in the eCTD?	CTD cross-references can be supported in the eCTD through the use of hyperlinks.	February 2003
3	Is it possible to change the values previously assigned to XML node attributes (e.g., the case where no value or the wrong value is placed in indication and later it is decided that a	Currently no. This question generated change requests 00200 and 00210.	February 2003

4	<p>It is very difficult to work out how to construct a valid index.xml file for the Control of Excipients section of Module 3 (3.2.P.4) without having to duplicate entries in the backbone and without deviating from the intended CTD structure. CTD expects that for each excipient a separate section 3.2.P.4.1 through 3.2.P.4.4 can be provided and that 3.2.P.4.5 and 3.2.P.4.6 are separate files. The eCTD cannot deliver a structure in which entries for 3.2.P.4.5 and 3.2.P.4.6 are not repeated either in the folder structure or as entries in the backbone.</p> <p>This question was generated by change request 00100.</p>	<p>One way to construct a backbone is as follows: Repeat the element m3-2-p-4-control-of-excipients for each excipient and assign the excipient attribute (e.g., magnesium stearate, and purified water) for each repeat. Under each of these include the leaf elements covering documents for 3.2.P.4.1, 3.2.P.4.2, 3.2.P.4.3 & 3.2.P.4.4. It is not necessary to include the leaf elements for 3.2.P.4.5 & 3.2.P.4.6 here. Then create another repeat of the element m3-2-p-4-control-of-excipients and assign the excipient attribute value 'animal-human-novel'. Include the leaf elements for 3.2.P.4.5 & 3.2.P.4.6 here.</p> <p>The directory/file structure may look something like this :</p>  <p>whilst the structure of the index.xml file would be like the image on the next page:</p>	February 2003
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<?xml version="1.0" ?>
<!DOCTYPE ectd:ectd (View Source for full doctype...)>
- <ectd:ectd xmlns:ectd="http://www.ich.org/ectd" xmlns:xlink="http://www.w3c.org/1999/xlink" dtd-version="3.00">
- <m3-quality>
- <m3-2-body-of-data>
- <m3-2-p-drug-product>
- <m3-2-p-4-control-of-excipients excipient="crosscamallose-sodium">
+ <m3-2-p-4-1-specifications>
+ <m3-2-p-4-2-analytical-procedures>
+ <m3-2-p-4-3-validation-of-analytical-procedures>
+ <m3-2-p-4-4-justification-of-specifications>
</m3-2-p-4-control-of-excipients>
- <m3-2-p-4-control-of-excipients excipient="magnesium-stearate">
+ <m3-2-p-4-1-specifications>
+ <m3-2-p-4-2-analytical-procedures>
+ <m3-2-p-4-3-validation-of-analytical-procedures>
+ <m3-2-p-4-4-justification-of-specifications>

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		<pre> - <ectd:ectd xmlns:ectd="http://www.ich.org/ectd" xmlns:xlink="http://www.w3c.org/1999/xlink" dtd-version="3.00"> - <m3-quality> - <m3-2-body-of-data> - <m3-2-p-drug-product> - <m3-2-p-4-control-of-excipients excipient="crosscamallose-sodium"> + <m3-2-p-4-1-specifications> + <m3-2-p-4-2-analytical-procedures> + <m3-2-p-4-3-validation-of-analytical-procedures> + <m3-2-p-4-4-justification-of-specifications> </m3-2-p-4-control-of-excipients> - <m3-2-p-4-control-of-excipients excipient="magnesium-stearate"> + <m3-2-p-4-1-specifications> + <m3-2-p-4-2-analytical-procedures> + <m3-2-p-4-3-validation-of-analytical-procedures> + <m3-2-p-4-4-justification-of-specifications> </m3-2-p-4-control-of-excipients> - <m3-2-p-4-control-of-excipients excipient="purified-water"> + <m3-2-p-4-1-specifications> + <m3-2-p-4-2-analytical-procedures> + <m3-2-p-4-3-validation-of-analytical-procedures> + <m3-2-p-4-4-justification-of-specifications> </m3-2-p-4-control-of-excipients> - <m3-2-p-4-control-of-excipients excipient="sodium-chloride"> + <m3-2-p-4-1-specifications> + <m3-2-p-4-2-analytical-procedures> + <m3-2-p-4-3-validation-of-analytical-procedures> + <m3-2-p-4-4-justification-of-specifications> </m3-2-p-4-control-of-excipients> - <m3-2-p-4-control-of-excipients excipient="titanium-dioxide"> + <m3-2-p-4-1-specifications> + <m3-2-p-4-2-analytical-procedures> + <m3-2-p-4-3-validation-of-analytical-procedures> + <m3-2-p-4-4-justification-of-specifications> </m3-2-p-4-control-of-excipients> - <m3-2-p-4-control-of-excipients excipient="animal-human-novel"> + <m3-2-p-4-5-excipients-of-human-or-animal-origin> + <m3-2-p-4-6-novel-excipients> </m3-2-p-4-control-of-excipients> </m3-2-p-drug-product> </m3-2-body-of-data> </m3-quality> </ectd:ectd> </pre>		
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5	Certain TOC tags are not required by the DTD. It is unclear if these need to be completed 1) always if possible 2) only if this element is repeated or 3) only if a regional authority requests it. Please clarify.	To be consistent with CTD general Q&A, always include these attributes as appropriate: - substance - manufacturer - product-name - excipient - indication - dosage form	February 2003
6	Appendix 4 provides specific folder names for some sections and states other sections can typically be submitted, as individual files. What is the definition of 'typically' and what should be done when they are not typical?	There are now clear definitions of what is recommended for the granularity of documents provided in the ICH guidance on 'Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use'. This describes what is considered to be the appropriate granularity for each section of the CTD and hence eCTD. Where there is no definition provided in the organisation document, applicants are free to construct the dossier as they see fit so long as it adheres to the conventions for folder and file naming described in the eCTD specification.	February 2003
7	Is there any control in the eCTD Specification over terminology to be used for indications?	No	February 2003
8	How will the reviewer view and use the “append” operation attribute? It would also be useful to have clarifications on how review tools within	The eCTD Specification is concerned with the transport of electronic CTDs from applicant to regulator. Consult regulatory authorities in each region on the electronic review tools each use to view this format.	February 2003
9	Will questions from Health Authorities be provided electronically using the specification?	The eCTD Specification provides a transport mechanism for one-way traffic from applicant to agency. This question generated change request 00220.	February 2003

10	It is recommended to have the name of the root folder to be the application number or registration number of the drug. Unfortunately, in some European countries companies don't get the application number prior to the submission. In the case of an MRP each country will give a different number creating an issue for naming the root folder. In some countries, the application number is given per pack size and/or strength, and the unique application number will be difficult to	Contact the regulatory authority for guidance.	February 2003
11	For the ID attribute, is it allowable to utilize an internal applicant identifier or would it need to be more understandable in order to support reasonable human identification (e.g. in reviewer to applicant correspondence about an issue).	The ID attribute is intended to be a unique reference within the submission that can be used to reference the item from another item within the XML document. XML requires the ID to begin with an alphabetic character. If an internal ID generator uses only numbers, appending a number to a leading alphabetic character that then could be used as the ID can create the ID.	February 2003
12	The eCTD Specification allows for one novel excipient in 3.2.A.3. What happens if there is more than one?	The regulatory authority should be consulted for a solution until the change request is resolved.	February 2003
13	The specification currently states that there is an eCTD empty folder template on the ICH website. One is not located there. Where is it? This question was generated by change request	A file which can be downloaded and run to create an empty eCTD folder template is now available on the ICH website.	July 2003
14	What is the position on the use of digital signatures within the eCTD? This question was generated by change request	Currently there are no plans for the M2 Expert Working Group to address this issue. Regional guidance should be consulted for the current use of digital signatures.	July 2003

15	<p>Are the filenames for documents referred to in Appendix 4 of the specification mandatory or optional?</p> <p>This question was generated by change request 00110 and 00120</p>	<p>Filenames in the eCTD are optional. The ones provided are highly recommended. To assist the reviewer when several similar files are open at the same time, it can be appropriate to consider alternative naming conventions that could provide unique, understandable filenames. The general provisions for naming of files are in Appendix 6 of the Specification.</p>	July 2003
16	<p>Can clarification be provided about the necessity to provide full text indices (eg. Adobe Catalogue files) and if desired by the agencies, how and where they should be included in the backbone?</p> <p>This question was generated by change request</p>	<p>Full text indices are not required by any of the ICH regional agencies and therefore the provision of guidance is not necessary.</p>	July 2003
17	<p>Would it be acceptable to introduce a level of sub-folders not described in the eCTD specification to assist the submission construction process?</p> <p>This question was generated by change request</p>	<p>Yes</p>	July 2003
18	<p>Should bookmarks be presented expanded or collapsed? Should bookmarks for tables and figures be separate structures?</p> <p>This question was generated by change request 00270</p>	<p>Insufficient experience is available across agencies to provide any formal guidance on this. It might not be considered appropriate to have all the bookmarks open since, in some instances, these can be so numerous that they are not useful to the review and it can affect 'refresh' time in a web-browser. Equally, it is probably not useful to have the bookmarks fully closed, since the reviewer would always have to open them. It is recommended, therefore, that the applicant considers the usefulness to the reviewers of how to present bookmarks and has some level of consistency across similar document types within the submission.</p>	July 2003

19	Can clarification be provided for what should be included as values for the 'font library' attribute? This question was generated by change request	At present, no agency intends to make use of this attribute and therefore provision of guidance is not necessary.	July 2003
20	Are .tiff files an acceptable format for provision within an eCTD submission or should they be converted to .pdf?	The .tiff file type is not supported within the eCTD specification. The section in the specification should be consulted (Appendix 7) relating to acceptable formats.	July 2003
21	When using the 'delete' operation attribute a checksum is required. Since no file is being provided to assign a checksum to, how should this checksum attribute be used?	It is recommended that a null entry be made in the checksum attribute, i.e., double quotation marks with no entry between ("").	July 2003
22	Is it feasible for legacy reports to continue to be submitted as a single file/document without being split into separate files/documents as per the M4 Organisation Granularity Annex. Is there a specific date from which all reports should be structured in the M4 Organisation Granularity Annex described way? This question was generated by change request	For study reports that have already been produced or are currently in the process of production, it is considered acceptable to submit these as a single file if this is the way that they have been created. It is recommended that new reports be created utilising the granularity described in the M4 Organisation Granularity Annex.	November 2003
23	Is the file name for an individual file fixed from beginning to end of life cycle? This question was generated by change request	No, except for names predefined in the eCTD specification or regional guidance, e.g. index.xml.	June 2004

24	Is the operation attribute for the regional (module 1) backbone xml file always new? This question was generated by change request	Refer to regional guidance.	June 2004
25	According to ICH E3 Structure and Content of Clinical Study Reports, the case report forms should be located in Appendix 16.3, the individual patient data listings in Appendix 16.4 and the publications and literature references in Appendices 16.1.11 and 16.1.12 respectively. The CTD organization provides locations for case report forms and individual patient data listings in Module 5.3.7 and for literature references in Module 5.4. Where should these items actually be placed in the CTD and the eCTD? This question was submitted to the CTD Implementation Coordination Group.	PDF files for case report forms and individual patient data listings should be organised by study in the folder for Module 5.3.7. However, in the <i>index.xml</i> file the leaf elements for the case report forms and individual patient data listings should be included under the same heading as other study report files with additional information included with any accompanying study tagging file. In addition, a repeat of the leaf element <u>can</u> be placed under the heading 5.3.7 Case Report Forms and Individual Patient Data Listings. Datasets, if required by the region, should be organised according to regional guidance. Files for publications and literature references should be located in the folder for Module 5.4. However, in the <i>index.xml</i> file the leaf elements for the publications and literature references <u>should</u> be included under the same heading as other study report files with additional information included with any accompanying study tagging file. In addition, a repeat of the leaf element should be placed under the heading for 5.4 Literature Re	June 2004
26	If an applicant submits an eCTD using Specification v3.0, how is forward compatibility with version 3.2 assured?	The recommendation is that applicants use the ID, even if using 3.0, to avoid future compatibility problems; For previously submitted files, consult with the Regulatory Agency to ascertain how to resolve the lifecycle issue.	June 2004

27	<p>Is it expected that one would stay with a given DTD version for the duration of an application, so that as long as submissions are made to the same application, one would use the same DTD version as for the original submission?</p> <p>Would - on the other hand - the expectation be that new versions of the DTD are applied within a certain time period, across all submissions regardless of whether they are new or ongoing? Also, if there is a need to change DTDs, how will the agency viewing tools present the cumulative view if there is a structural change to the submission eg. renaming of old sections, introduction of new sections etc.</p>	<p>Applicants are expected to use the current DTD as accepted in the individual regions. The M2 Expert Working Group and the agencies of the three regions will provide guidance on when to use new releases. The timing of the implementations of new releases will be determined as required. Regulatory changes (e.g. changes in the CTD) might have to be implemented immediately, while technical changes might be delayed to major new releases.</p>	November 2004
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28	<p>Clarification should be provided by all ICH regions as to whether node extensions can be used in Modules 2-5</p> <p>The ICH spec allows node extensions to be used in Modules 2-5 and their use in Module 1 is a regional matter. FDA states that node extensions are not supported in any part of the submission and this therefore invalidates the ICH spec. Experience on production of submissions for Europe demonstrates that node extensions are required to deliver a navigable structure for Modules 4 and 5. At present this means that eCTDs are not re-usable across regions and thus will create significant amounts of rework for industry. FDA should accept node extensions in</p>	<p>The use of node extensions should be discussed with FDA on a case by case basis. Other regions are able to accept appropriate use of node extensions in compliance with the eCTD specification (i.e. their use is discouraged unless there is no other feasible means to submit the information). Refer to EU and MHLW regional guidance for specific instances where it can be used.</p>	<p>November 2004</p> <p>May 2005</p>
29	<p>Can a single, global eCTD submission be constructed and transmitted to multiple regions, with each regional authority ignoring or deleting other regions' submission material?</p>	<p>This is not advised.</p>	<p>May 2005</p>
30	<p>Are applicant provided style sheets allowed?</p> <p>The question was generated by change request</p>	<p>Consult regional guidance</p>	<p>May 2005</p>
31	<p>Is a regional MD5 checksum file (xx-regional-md5.txt) needed?</p> <p>The question was generated by change request</p>	<p>Not needed, index.xml includes the checksum for this file.</p>	<p>May 2005</p>

32	Japanese characters are 2 bytes. Can 64 characters still be used for file/folder names in Japanese?	The Specification 3.2 does not allow for Japanese characters in folder and file names.	May 2005
33	Do submission sequence numbers have to be consecutive, i.e., 0005 must be submitted after 0004?	For Japanese submissions, sequential numbering is required. For all other regions, it is preferred, but not required. For all regions, sequence numbers should be unique within the overall application.	May 2005
34	Can the operation attribute 'new' be used in subsequent submissions where there is already a file in the same node? The question was generated by change request 00820	Yes, but there might not be many opportunities in Modules 2-5, where this could apply. This might be more applicable in Module 1 with items such as cover letters and application forms. Refer to table 6-3 of the Specification 3.2 for the appropriate use of the operation attribute.	May 2005
35	Can further clarification be provided on the related sequence element? The question was generated by change request	Related sequence is used differently across the regions. Consult regional guidance for details.	May 2005
36	From the eCTD experience of the IWG, what parts of the Specification are commonly misinterpreted that would prevent my eCTD message from being viewed by another applicant/regulator?	Based on experience, there have been different interpretations of the eCTD Specification that have prevented timely exchange of eCTD submissions. Those creating and viewing eCTD messages should adhere to the eCTD Specifications (ICH and regional) and consult with regional authorities to avoid these problems. The items in the following list already exist in the Specification 3.2, but have been summarized here to alleviate these problems. Adherence to these items is technically necessary to exchange eCTD messages. Extra controls might hinder the exchange of eCTD messages. The IWG will continue to monitor eCTD implementation to provide additional clarity.	May 2005

Q&A No. 36

1	Ensure there is an ICH backbone file named index.xml in the sequence folder
2	Ensure ICH published checksum(s) of eCTD DTD is the same as checksum of eCTD DTD in 'util/dtd' folder
3	Ensure the index.xml is validated against the corresponding eCTD DTD version in the 'util/dtd' folder
4	<p>Ensure the eCTD index.xml is validated for logical and correct attribute content as defined in the ICH eCTD specification as follows:</p> <ul style="list-style-type: none"> - If the value of the operation attribute is new, then the modified-file attribute value is empty or not provided - If the value of the operation attribute is append, replace or delete, then the modified-file attribute will have a valid value - If the operation is new, append or replace, then the attribute xlink:href will have a valid value - Verify that the ID attribute value starts with a letter or underscore character
5	Ensure there is a xx-regional.xml[1] in the appropriate folder
6	Ensure regionally published checksum(s) of the DTD, Schema, and related files are the same as checksums of the corresponding files in the 'util/dtd' folder.
7	Ensure the regional index files are validated against the corresponding regional DTD, Schema, and related files (e.g., mod files) in the 'util/dtd' folder.
8	If using regionally required instance files (e.g., STF), ensure regionally published checksum(s) of the DTD, Schema, and related files are the same as checksums of the corresponding files in the 'util/dtd' folder.
9	If using regionally required instance files (e.g., STF), ensure the instance files are validated against the corresponding regional DTD, Schema, and related files in the 'util/dtd' folder.
10	Ensure the regional xml file (s) is validated for correct XML syntax and correct attribute content (consult regional guidance)
11	Ensure the checksum for every file is equal to the associated checksum stated in the relevant backbone (i.e., index.xml, xx-regional.xml)
12	Ensure all the files identified by an xlink:href reference exist.
13	Ensure there are no unreferenced files in folders m1 through m5 (including subfolders other than 'util' subfolders)
14	Ensure the appropriate format is used for the modified file attribute in relation to the DTD being referenced. (Specification 3.0 vs. Specification 3.2)
15	Ensure that all file and folder naming conventions (length limits and allowable characters) comply with Appendix 6 of the eCTD Specification (Note: Folder and file names in the eCTD Specification are highly recommended, not mandatory (see Q&A No. 15))
16	Ensure that all the lowest level heading elements included in the submission contain at least one leaf
17	Ensure no PDF files are larger than 100 megabytes
18	Ensure that sequence numbers have 4 digits (i.e., numbers between 0000 and 9999)
19	Ensure that the sequence folder name matches the sequence number in xx-regional.xml (not applicable in Japan)
20	Ensure that leaf or node extension Title attribute is not empty (except when the operation attribute is delete)
21	Ensure no files have file level security or password protection enabled
22	Ensure that the PDF Links and bookmarks are relative
23	Ensure that PDF files have been optimized for fast Web delivery

[1] Where xx represents the ICH region designator: eu for European Union; jp for Japan; us for United States regions

eCTD Specification Change Requests (received after the release of Step 4)

#	Requestor	M2 Sponsor	Specification Component	Description	Comments	Status	Action
00010	CTD-E FDA	FDA	m5-3-5	Multiple Indications	Resolved by CTD group, no implication for eCTD	Out of scope	
00020	Liquent	EFPIA FDA	4-62 (#371)	4-62 (#371) shows that DTDs and style sheets should be put in a dtd or style subfolder but on page 6-2 it shows that dtd files should be placed directly under util folder. Which is correct?	Appendix 4 is the definitive source of information, it should be made sure that it is corrected in the next version	Approved for specification change	Specification changed to Version 3.2
00030	EFPIA	EFPIA FDA	Page 4-8, Line 34	Incorrect use of hyphen	Must be changed	Approved for specification change	Specification changed to Version 3.2
00040	MHLW	MHLW	Page 2-5	Parta (UPPERCASE is not allowed) – not necessary to restrict to lower case	It is best to leave it as it is (lower case)	Rejected	
00041	MHLW	MHLW	Page 4-1	Full path of the File/Directory. Page 6-5 ...Use the full path to refer to files. The full path is not shown in these	Not relevant	Rejected	
00042	MHLW	MHLW	Page 6-5	Use the full path to refer to files. The full path is not shown in these	Not relevant	Rejected	
00050	Liquent	FDA	3.2.A.3	Request 3.2.A.3 to be changed to a repeating element	Understood and will address in Q&A (No. 12) and then next version of DTD	Approved for specification change	Specification changed to Version 3.2

00060	FDA	FDA	Appendix 3, footnote 6	States that there will be as many subfolders as there are studies included There may be some studies in Section 5.3 without patient data listings or	Erroneous question, text in footnote is correct; question not relevant	Rejected	
00070	EFPIA	EFPIA FDA	ich-ectd-3-0.dtd	the element declaration <!ELEMENT m3-2-p-2-1-components-of-the-drug-product ((leaf node-extension)?)> is different to all other element declarations: <!ELEMENT name ((leaf node-extension)*)>	Element is no longer in the 8 October version of the dtd; not relevant any longer	Rejected	
00080	ECTD IWG	FDA	Header	Updated Version Number	Not relevant, version in header is correct	Rejected	
00090	EU	FDA	6-9 and 6-13 Table 6-8	Acrobat 5 is specified when it should read “PDF 1.3”	Change the examples (such as PDF 1.2 or PDF 1.3) in the specification to include both the ‘application version’ and the ‘file type’ version. Also, include some of this in Appendix 7	Approved for specification change	Specification changed to Version 3.2
00100	EFPIA EU	EFPIA EU	3.2.p.4	Structure of the DTD to support excipients is less than optimal	DTD will be updated, also addressed in Q&A No. 3	Approved for specification change	inform CTD Q; change next major release

00110	EFPIA EU	EFPIA EU	Appendix 3, 4	Clarify file names mandatory or optional. Inconsistent wording	Clarification is highly recommended; Q&A (No. 15) recommended before rewriting agreed that file names are optional	Approved for specification change	Specification changed to Version 3.2
00120	EFPIA EU	EFPIA EU	Appendix 4	Recommendation for the use of unique filenames where reviewers are likely to have several files open for comparison.	Unique file names as general principle will be recommended – related to Q&A of 110	Approved for Q&A	No. 15
00130	EFPIA EU	EFPIA EU	DTD – Appendix 6 Example	Use of the checksum; clarify use of checksum when delete operation is applied	Needs to be addressed in a Q&A (No. 21) Checksum should be Null	Approved for Q&A	No. 21
00140	EFPIA EU	EFPIA EU	Appendix 4, Section 3.2.S.2	Suggest optional use of sub folders to better structure documents	As all file and folder names are optional, this is allowed	Approved for Q&A	No. 17
00150	EFPIA	EFPIA	Appendix 4	States that the regional DTD and xml files have one naming convention, but the EU Module 1 has a different naming convention. Which takes	EU has been changed, not relevant any longer	Out of scope	
00160	EFPIA EU	EFPIA EU	Appendix 4 3.2.P.7	Suggest multiple files allowed for different container closure systems.	Flexibility over number of files to be included in revised M4 Organization document see 00440	Approved	M4 organisation document changed
00170	EFPIA	EFPIA	DTD	Use of “Title” attribute within structural elements of the DTD.	No “Title” attribute for the structure	Approved for specification change	consider structure representation and control as part of next major release
00180	JPMA	JPMA		Preliminary discussions on how to handle multiple indications	Duplication, see 00010	Out of scope	

00190	ECTD IWG		Cover Page	Add "International"	Needs to be changed	Approved	Cover page was changed
00200	Q&A		DTD	Make the indication attribute required	Change in DTD and specification necessary	Approved for specification change	Specification changed to Version 3.2
00210	Q&A		DTD	Need to consider how to update index.xml when there is an error in the backbone	Answer: should be consulted with regulatory agency	Approved for Q&A	No. 3
00220	Q&A	EFPIA		The specification be expanded to support two way communication		Out of scope	
00230	FDA	FDA	2-3 Checksum	Detailed explanation on using checksums when deleting a previously	Not relevant as duplication to 00130	Rejected	
00240	FDA	FDA	Page 6-7	Make leaf ID required in eCTD Specification (at present is optional)	Change specification to make leaf ID required at leaf level	Approved for specification change	Specification changed to Version 3.2
00250	EFPIA	EFPIA		Zip files. A realistic mechanism to parcel up a small eCTD submission and attach to an email or simple FTP transmission is required. .zip is one simple option for the bundling together of the files within the directory structure required for an eCTD submission and hence being able to provide a single object to the agency in	Zip is OS dependant, open standard archiving formats may be considered. Out of scope for IWG	Out of scope	

00260	EFPIA	EFPIA		<p>Clarification should be given, with examples as to the intended content of the attribute 'application version'.</p> <p>The specification defines an attribute termed 'Application Version' but provides no examples of what might be used here. For example, is 'Acrobat v5' okay or should it be PDF v1.3. Other examples might relate to Word version when .rtf files are used reginally etc. It would be useful to understand the purpose of this attribute and hence what to use as valid terms.</p>	Duplication, see 00090	Approved for specification change	Specification changed to Version 3.2
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00270	EFPIA	EFPIA		<p>Should bookmarks be presented expanded or collapsed? Should bookmarks for tables and figures be separate structures?</p> <p>Several options exist regarding the presentation of bookmarks. Firstly the bookmarks can be presented so that they are collapsed to the first level whereby the reviewer can expand those that they wish to explore or they can be presented fully expanded so that the review can see all the bookmarks but this may be a very long list in some documents. Secondly, the bookmarks can be presented sequentially, page by page, or they could be grouped with Tables and Figure appearing separately. Is there a preference form</p>	<p>Not sufficient experience yet for a firm answer across the regions.</p> <p>Suggestion that it is a company decision for the individual submission</p>	Approved for Q&A	No. 18
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00280	EFPIA	EFPIA		<p>The specification should be developed to encompass a definition for acceptable digital signatures</p> <p>Several companies are wishing to move towards the use of digital signatures but there is no commonly defined acceptable standard and/or statement regarding signatures from ICH. ICH would be a sensible forum for such a standard to emerge. This should be taken on as a change control item but in the meantime some form of guidance through Q&A would be useful eg. what to do if you do have digital signatures – are they acceptable and what constitutes acceptability.</p>	<p>Appropriate for a short Q&A (No. 14) stating that there is no position on this point</p>	Out of scope	
00290	EFPIA	EFPIA		<p>The current upper limit of file size should be raised from 50MB. The original requirement for a maximum file size for pdf files of 50MB came from the initial FDA guidance document dating from 1998. Performance of networks and pcs has increased significantly from then. ICH should consider increasing the maximum file size to something larger. This will facilitate the preparation of documents – particularly legacy documents where scanning has been the only option.</p>	<p>Test whether file sizes of 100 and 75 MB can be accommodated by all regions</p> <p>Has been tested and can be accommodated in all regions</p>	Approved for specification change	Specification changed to Version 3.2

00300	EFPIA	EFPIA		<p>Clarification should be given, with examples as to the intended content of the attribute 'font library'.</p> <p>The specification defines an attribute termed 'font-library' but provides no examples of what might be used here. For example, is 'Arial' appropriate or would it need to be 'Arial, Arial Black, Arial Narrow, Arial Italic' etc. It would be useful to understand the purpose of this attribute and hence what to use as valid terms.</p>	This it currently not used	Approved for Q&A	No. 19
00310	EFPIA	EFPIA		<p>Can clarification be provided about the necessity to provide full text indices (eg. Adobe Catalogue files) and if desired by the agencies, how and where they should be included in the backbone.</p>	<p>There are no current plans to use Full Text Index in any of the regions. The section on providing pdf indexing requirements will be revisited in the next version of the specification; also Q&A No. 16</p>	Approved for specification change	Specification changed to Version 3.2
00320	EFPIA	EFPIA		<p>When an update occurs to a file, other documents may have redundant and inaccurate links to it. A mechanism should be established to manage either the redirection of this link and/or the highlighting that the link is pointing to a superceded document and the review tool(s) offers the updated document as</p>	See change request form	Deferred	until more experience with lifecycle management of eCTDs

00330	EFPIA	EFPIA		The DTD should be modularised. For example, the leaf, so it can be used for other purposes such as in the regional module.	Harmonizing the technical approach to Module 1 with the other Modules of the eCTD is planned for the next major release of the eCTD	Approved for specification change	Specification changed to Version 3.2
00340	EFPIA	EFPIA		Additional operation attribute to be included in the spec to allow for the ref of a file from multiple places in the backbone but the mgmt of full attribute information only once. It is appropriate to make ref to the same file from many locations. In the eCTD the principle should be that the file is included only once but can be linked to from multiple locations in backbone. This is a good solution except when lifecycle means that this document is, e.g., replaced. Under this circumstance, each entry into backbone must be individually updated. The eCTD should include an option to provide a 'reference' operation attribute. For a new submission, primary location of a file would have the full metadata associated with it but at secondary locations, metadata could refer to the primary location in the backbone. Thus, when updating, it would only be necessary to update the operation attribute at the primary location, thus simplifying lifecycle maintenance and leading to the reduction of potential errors that would	When the leaf ID will be mandatory (see 00240) this can be used to provide a reference to the primary entry in the backbone. Explanatory notes will need to be provided on how to utilize the leaf ID e.g. when multiple instances of a document are required.	Approved for specification change	Specification changed to Version 3.2

00350	EFPIA	EFPIA		<p>Are .tiff files an acceptable format for provision with an eCTD submission or should they be converted to pdf?</p> <p>tiff is a commonly used format for scanned documents – particularly legacy documents and CRFs.</p>	No, consult the section of the specification for acceptable formats	Approved for Q&A	No. 20
00360	EFPIA	EFPIA		<p>The GxP requirements for signatures needs to be considered in the context of provision of multiple files for a study report – and in particular as it relates to an updated document.</p> <p>Under GCP and GLP signatures are required and in a paper process these cover the whole report. So in an initial submission the signature provided in a report can be taken to cover the whole report and is contemporaneous. However, once into the lifecycle management process electronically, it is possible to update only certain files eg. a new appendix. Guidance needs to be provided regarding the GxP interpretations of signature applicability – namely when do signatures also need to be updated and how should the process be designed to demonstrate exactly what each version of a signature actually applies to.</p>	Has been taken to the CTD Coordination group November 2003	Out of scope	

00370	FDA/PhRMA	FDA	ich-stf-stylesheet-1-0a.xsl internal:vocabulary41eaf-labels-file-tag	<p>Change <item>randomisations-scheme</item> to <item>randomisation-scheme</item> and <item>iec-erb-consent-form-list</item> to <item>iec-irb-consent-form-list</item></p> <p>Use the singular form, randomisation, not the plural form of the word.</p> <p>Correct a probable error in the iec-irb-constant-form-list value.</p>	Requestor asked to drop change request	Rejected	
00380	EFPIA	EFPIA	Appendix 4	Where optional granularity is allowed the specification only defines file name at the lowest level. Advice should be given regarding what file names to use at the higher level.	Reference is made in the Specification to the M4 granularity document	Approved for specification change	Specification changed to Version 3.2
00390	FDA/EFPIA	FDA/EFPIA	Page 2-1	Currently states that ICH Web has empty template. No template exists	Empty folder structure will be provided	Approved for Q&A	No. 13
00400	EFPIA	EFPIA	Appendix 9	The page numbering in Appendix 9 of the Specification is incorrect. It starts with 9-14 and should be 9-1.	Minor change, can be made at next edit.	Approved for specification change	Specification changed to Version 3.2
00410	FDA	FDA	Tracking Table	Close 00180 and delete text in first paragraph of description column	Requestor asked to drop change request	Rejected	

00420	Boehringer Ingelheim Pharmac. Inc.	FDA	Appendix 4: File Organization for the eCTD	We recommend that all sections of the eCTD Quality Module 3 be allowed the option of containing a single document or multiple documents in each section and subsection. We agree that once a particular approach has been adopted (single or multiple documents), it should be maintained for the life of the dossier.	Single or multiple documents/files are already allowed in the eCTD. The eCTD Specification (appendix 4) needs to be updated and will be done at the next specification change.	Approved for specification change	Specification changed to Version 3.2
00430	Boehringer Ingelheim Pharmaceuticals Inc	FDA	Appendix 4: File Organization for the eCTD	The “2.3 Introduction to the Quality Overall Summary” (Item 11 in the eCTD File Organization) is redundant to the “2.2 CTD Introduction” (Item 10 in the eCTD File Organization). We recommend that the “2.3 Introduction to the Quality Overall Summary” be deleted from the eCTD	Not in scope of eCTD, as it is a content issue. Discussion with CTD Q confirmed that there is no need for change, as the placeholder is already there in the CTD Q document. If the numbering is corrected in the CTD Q document, the eCTD will make this change as well.	Rejected	
00440	FDA	FDA	DTD and Specification	Consider inclusion of Container/Closure system as an attribute		Deferred	until more experience with CTD
00450	FDA	FDA	Specification v3.0, pages 6-3 through 6-9 and 8-2	Ensure that approved change request #00240 is the currently accepted way all regions are using Leaf ID with the modified file attribute.	Change specification to make leaf ID required at leaf level	Approved for specification change	Specification changed to Version 3.2

00460	EFPIA	EFPIA	STF specification & M4 Granularity Annex	Is it feasible for legacy reports to continue to be submitted as a single file/document without the need for splitting up into separate files/documents as per the STF and the Granularity Annex. Is there a specific date from which all reports should be structured in the CTD defined way?	Mixed submissions (legacy as one file and reports written according to STF) are acceptable at the moment. A time frame for the transition will have to be defined	Approved for Q&A	No. 22
00470	EFPIA	EFPIA	Specification v3.0 & M4 Granularity Appendix	GLP and GCP inspectors expect to see consecutive page numbers across a report. CTD and eCTD allow page numbering by document/file. The two are incompatible.	Has been taken to the CTD Coordination group November 2003	Out of scope	
00480	JPMA	JPMA	Specification v3.0, Appendix 5	The listing of media types for eCTD submission is not necessary. M2 recommendation on physical media and regional guidance should be referred to instead.	Correct at next specification change, section 5-2	Approved for specification change	Specification changed to Version 3.2
00490	JPMA	JPMA	Template Empty Folder Structure	Errors in template of empty folder structures	Update template folder structure	Approved	Empty Folder structure was updated Version 3.03
00500	JPMA	JPMA	Specification v3.0, Appendix 3	Errors in Appendix 3, Fig 3-3 and 3-4		Approved for specification change	Specification changed to Version 3.2
00510	JPMA	JPMA	Specification v3.0, Appendix 4	Inconsistency between line 23 and line 24 of Appendix 4 in the abbreviation of pharmacology	Correct line 24 to pharmacol	Approved for specification change	Specification changed to Version 3.2
00520	JPMA	JPMA	Specification v3.0, Appendix 2	The 256 maximum for length of path does not allow regulators to add to that path, if needed	Change page 2-4 the maximum length to 230 to allow regulators to add server names to the path (page 2-4)	Approved for specification change	Specification changed to Version 3.2

00530	ICH M2 IWG	ICH M2 IWG	Specification v3.0, Table 6-3	Clarify the operation attributes REPLACE and APPEND	Correct specification	Approved for specification change	Specification changed to Version 3.2
00540	EFPIA	EFPIA	Specification v3.2	<p>For a submission that has been filed utilising v3.0, is it possible to move to v3.2?</p> <p>Comment from vendors: "Some sponsors have already sent submissions using 3.0 and but may not realize that they have to stick with 3.0 for the rest of that applications life cycle as introduction of ID's and use of ID's in modified file attribute won't allow sponsors to change over to 3.2". Is this true and if so, what is recommended by the agencies? It does not seem practical to stay with an old version forever. Can this situation be rectified and how can it be avoided in future when the specification is updated again?</p>	<p>The recommendation is that the ID is mandatory, even if using 3.0, to avoid compatibility problems;</p> <p>For previously submitted files, consult with the Regulatory Agency to ascertain how to resolve the lifecycle issue.</p>	Approved for Q&A	No. 26

550	EFPIA	EFPIA	Specification v3.2	<p>Clarification should be provided regarding any restrictions to character sets in the id value. According to the W3C definition an ID attribute value uses the "name" definition and must start with either a letter, an underscore or a colon and then can be followed by any combination of letters (upper or lower case), digits, period, hyphen underscore or colon. FDA has recently returned a pilot eCTD submission to J&J because the ID attribute value contained an underscore character. They stated that the syntax for the ID attribute must match the syntax of the file name (as specified in the ICH eCTD spec this means lower case letters, digits and hyphens only). They said the ICH spec stated this syntax for the ID attribute quoting page 2-4 and 2-5 of the version 3.2 spec as the basis for this statement. They also said the ID could not contain an underscore as it was being used in hyperlinks, and may be disguised by the formatting of the linking text (if it uses an underline). These two specs are not</p>	FDA agrees that underscores can appear in the leaf id, as long as it is not the first character	Rejected	
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560	EFPIA	EFPIA	Specification v3.2	<p>Clarification should be provided by all ICH regions as to whether node extensions can be used in Modules 2-5. The ICH spec allows node extensions to be used in Modules 2-5 and their use in Module 1 is a regional matter. FDA states that node extensions are not supported in any part of the submission and this therefore invalidates the ICH spec. Experience on production of submissions for Europe demonstrates that node extensions are required to deliver a navigable structure for Modules 4 and 5. At present this means that eCTDs are not re-usable across regions and thus will create significant amounts of rework for industry. FDA should accept node extensions in Modules 2-5.</p>	<p>FDA has concerns that node extensions might be over-used. Experience during the testing phase has confirmed the validity of these concerns. In many instances, the requirement for STF in the US eliminates the need for node extensions. There may be some occasions where the use of node extensions could be justified, and that should be discussed with FDA on a case by case basis. For the time being, other regions are able to accept appropriate use of node extensions in compliance with the eCTD specification (i.e. their use is discouraged unless there is no other feasible means to submit the information). The IWG will review this situation.</p>	Approved for Q&A	No. 28
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570	EFPIA	EFPIA	Stylesheet	<p>The ICH standard stylesheet does not adequately support the use of node extensions – the display is corrupted. The ICH spec supports the use of node extensions at the lowest level. When node extensions are used, the stylesheet does not display the title of the file correctly. All files under that node extension are included in the title for each file. The attached screenshots demonstrate the issue.</p> <p>Slide 1: xml source code</p> <p>Slide 2: display in style sheet. Text in yellow box should be m5351 (plus node extension detail, ideally)</p> <p>Slide 3: As displayed in the latest version of The DataFarm viewer(attached PPT slides)</p>		Approved	Stylesheet was rewritten
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580	EFPIA	EFPIA	Specification v3.2	There are significant incompatibilities between the output of certain eCTD builder and viewer tools because of differences of interpretation of the spec and differing items being validated. ICH should develop a validation suite. Recent experience within Europe (and US) has highlighted that the 'valid' output of one vendor product is not necessarily valid as input to another. This is leading to the need to test and correct submissions before filing. The incompatibilities are arising because one product is expecting certain items to be addressed in particular ways (although a specific way is not stated in the eCTD spec). This has led to incompatible interpretations. This could be avoided if a suite were to be developed by ICH which could be used by all tools.	The issue has been recognised. 1st step is to define the criteria that the various vendors use for validation.	Approved	Validation criteria will be published on ICH website by the end of the year as a Q&A
590	Datafarm Inc.	PhRMA	Specification v3.2	Is the file name for an individual file fixed from beginning to end of life cycle?	Answer in the negative	Approved for Q&A	No. 23

600	Datafarm Inc.	PhRMA	Specification v3.2	<p>Regional XML reference in INDEX.XML</p> <p>According to DTD and spec all documents submitted within the submission should have a reference (leaf) within the XML backbone. When amendments, variations, etc. are sent the appropriate Operation and modified file attributes should be used to maintain the life cycle of that document. Does this rule apply to the leaf that refers to regional XML file? Please note even though the actual document is controlled by the regional authorities the reference and life cycle management of this leaf/document lies within the ICH DTD.</p>		Approved for Q&A	No. 24
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610	Datafarm Inc.	PhRMA	Specification v3.2	<p>Application Form and Cover Letter Life Cycle...</p> <p>According to DTD and spec all documents submitted within the submission should have a reference (leaf) within the XML backbone. When amendments, variations, etc. were sent the appropriate Operation and modified file attributes should be used to maintain the life cycle of that document. Does this rule apply to the leaf that refers to Application Form and Cover Letter that exists in all sequences? Also, this is something that is common across regions. Please note even though the actual document is controlled by the regional authorities it will be nice to have a common set of guidelines as they are common across regions.</p>	<p>Refers to specific regional documents within Module 1. Consult regional guidance.</p>	Out of scope	
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620	Datafarm Inc.	PhRMA	Specification v3.2	<p>Text file with MD5 Value and cover letter...</p> <p>The MD5 value for index.xml in a Text file is clearly specified in the spec. Still it led to some confusion with interpretation. Please clarify:</p> <ol style="list-style-type: none"> 1. There is only one index-md5.txt with index.xml md5 value stored within that file per sequence and it stays along with index.xml. 2. There is no need for index-md5.txt for regional xml file as this MD5 value is already present in the index.xml 3. It is impossible to generate the MD5 value and place that value in the cover letter (page 5-2). This will change the MD5 value of the cover letter, regional xml and index.xml. May be this can be placed on the Media Label. 	<p>In appendix 5, the eCTD Specification requires a paper cover letter that is also to be submitted as a pdf (cover.pdf) not linked to the backbone. This is the cover letter to which the md5 text is to be added as an appendix. These matters are also dealt with in regional guidance.</p>	Deferred	For clarification in the next version of the specification
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630	Datafarm Inc.	PhRMA	Specification v3.2	<p>The ID value requirement is not clear and requires additional specifications. Per ICH specifications on page 6-8 it states...“Unique identifier for this file in the XML instance. Leaf ID must start with a character.”</p> <p>It will be nice if this clearly states that ID value should:</p> <ul style="list-style-type: none"> -Start with alpha character -Only alpha and numeric values are allowed and no symbols or special characters -No spaces are allowed -Length of the ID value should not exceed "n" characters <p>Regional review systems have their own limitations in terms of length of the leaf attribute values such as title. It will be nice if ICH controls these just like they are controlling href maximum length and file name maximum length.</p>	With the exception of the requirement that the id must start with an alpha character, there are no limitations on the contents of these fields, subject to technical limitations.	Rejected	
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640	GSK	EFPIA	Specification v3.2	<p>There is an inconsistency in the description of the maximum file size</p> <p>Appendix 7: Specification for Submission Formats of the eCTD, page 7-1:</p> <p>the guidance states: "To ensure that PDF files can be accessed efficiently, PDF files should be no larger than 100 megabytes." However, on page 7-4 of the eCTD Specification, under Page Numbering, the guidance states "Two exceptions to this rule can occur (see details in the guidance for the modules of the CTD. First, where a document is split because of its size (e.g., >50MB), the second or subsequent file should be numbered consecutively to that of the first or preceding file."For consistency, the latter occurrence should be updated to 100MB.</p>	<p>This is a typographical error in the specification. The maximum file size is 100 MB, not the 50 MB given in the example.</p>	<p>Approved for specification change</p>	<p>next major release</p>
650	Centocor BV	EFPIA	Specification v3.2, Appendix 4, file organization for Module 3.2.S	<p>File organisation to support manufacturer should be consistent across Modules 2.3.S, 2.3.P, 3.2.S and 3.2.P. At present 3.2.S. is subdivided per substance/manufacturer, 3.2.P has only subdivision by product while 2.3.S and 2.3.P have no subdivisions. Can subdivisions for manufacturer in all sections be defined? See also change request 660</p>	<p>For Modules 2.3.S and 2.3.P it is already possible to differentiate by manufacturer, by the file name & by attributes.</p> <p>For Module 3.2.P, refer to CTD Q how they see the organisation of 3.2.P and its subsections.</p>	<p>Rejected</p>	<p>Refer second part to CTD Q</p>

660	Centocor BV	EFPIA	Specification v3.2	File organisation for 3.2.P should follow the same principles as for 3.2.S. with respect to differentiation between manufacturers. 3.2.S has a folder organisation by substance/manufacturer, 3.2.P has no such organisation below product. A folder structure should be introduced for each manufacturer.	Refer to CTD Q to determine how they want the organisation of 3.2.P and its subsections.	Out of scope	Refer to CTD Q
670	Centocor BV	EFPIA	Specification v3.2	<p>To prevent maintenance of identical copies of documents, it should be possible to make a link to the appropriate document elsewhere in the same submission or any of the previous submission in the eCTD life cycle. Examples are given in the original change request.</p> <p>This could be achieved if an additional operation attribute (e.g. "link") is allowed, next to new, append, replace, delete.</p>	<p>A file should only be included once within a single sequence.</p> <p>The requirements for references to one file across sequences are different in each region.</p> <p>The eCTD EWG will address the "link" concept as it relates to single sequences as part of lifecycle in the next major release.</p>	Deferred	Next meeting
680	Aventis	JPMA	ICH eCTD Style Sheet	ICH eCTD Style sheet cannot work for "Node-Extension" xml-instance		Approved	Stylesheet was rewritten

690	GSK	EFPIA	Specification v3.2	<p>Moving to a new version of a specification during the lifecycle of a product.</p> <p>Do you expect that we would stay with a given DTD version for the duration of an application, so that as long as we are submitting to the same application we would use the same DTD version as used for the original submission, or would we be expected to apply new versions of the DTD within a certain time period, across all submissions regardless of whether they are new or ongoing?</p> <p>Also, if there is a need to change DTDs, how will the agency viewing tools present the cumulative view if there is a structural change to the submission eg. renaming of old</p>		Approved for Q&A	No. 27
700	Lorenz	EFPIA	Specification v3.2	<p>Can an eCTD be submitted that covers more than one region?</p> <p>If the content of Modules 2-5 in a submission is to be the same between two or more regions is it allowable to submit more than one Module 1 in the same eCTD?</p>		Approved for Q&A	No. 29
710	Lorenz	EFPIA	Specification v3.2	<p>Are vendor specific style sheet allowed? Style sheets may include function to redirect reference links to</p>		Approved for Q&A	No. 30

720	Lorenz	EFPIA	Specification v3.2	Is an MD5 value required for the regional index file Are regional MD5 checksum files (##-regional-md5.txt) mandatory, optional or not allowed?		Approved for Q&A	No. 31
730	Lorenz	EFPIA	Specification v3.2	Japanese characters are two bytes. Can 64 characters still be used for file/folder names in Japanese?		Approved for Q&A	No. 32
740	Lorenz	EFPIA	Specification v3.2	Clarification of the allowable leading character of the 'id' attribute. Table 6.8 of the specification defines that the id value should start with a character. This is perhaps imprecise since a character could be alpha, numeric, or other. Numeric is not allowable according to W3C definitions. Could a more precise definition be provided as to what are	see Q&A No. 11	Rejected	
750	Lorenz	EFPIA	Specification v3.2	What length of 'title' attribute is allowable/recommended? The Title field appears to have no restriction to the number of characters. Since the titles of documents such as study reports can often be several hundred characters, could guidance be given whether there is actually any restriction and whether a full title is of value to the reviewer or whether a shortened form should be used?	Propose 1024 bytes - to be checked in caucus meetings on Monday	Approved for specification change	

760	Lorenz	EFPIA	Specification v3.2	Do submission sequence numbers have to be consecutive eg. 0005 always has to be submitted after 0004 or are there circumstances where 0005 can be submitted before 0004?		Approved for Q&A	No. 33
770	AstraZeneca	PhRMA	Specification v3.2 See page 6-11, "Instructions for Submitting Sections as Paper."	Please can you clarify whether the contents of the Application-Version field, reference the PDF version or the Acrobat Version (e.g. PDF Version 1.4, or Acrobat 5)?	We have already addressed this as a change request (#00090) where our response is that it should be the PDF version. It looks like some Acrobat version numbers are still given. We'll need to correct that properly at the next edition.	Approved for specification change	
780	AstraZeneca	PhRMA	Specification v3.2 See "Methods for Creating PDF Documents and Images."	Scanning Standards - is it possible to scan at 600 dpi, instead of the ICH recommended 300 dpi? Kanji documents look unclear when scanned at 300 dpi.	Specification should be changed to 'at least 300 dpi'.	Approved for specification change	
790	AstraZeneca	PhRMA	Specification v3.2 See "Instructions for an Amendment, Supplement, or Variation."	Standardisation of PDF Global Acrobat Specifications - What plans are there to standardise the PDF Global Acrobat Specifications for eCTD (e.g. Distiller settings)? What are the PDF settings upon distilling the PDF: what version (1.3?), is the PDF optimised? Does the PDF have thumbnails?	The PDF section of the eCTD specification addresses standardization across all regions; use of PDF or XML will be evaluated for next specification.	Rejected	

800	AstraZeneca	PhRMA	Specification v3.2 See page 6-11	Placebo and Comparators - in applications for clinical trials, where should the CMC information on Placebo and Comparators be located? For example, treat each placebo and each comparator as separate 3.2 Drug Products within the application OR include both placebo and comparator	This is a CTD Q question, it will be handed over to the CTD Q group.	Rejected	
810	EFPIA	EFPIA	Q&A 28	Could the eCTD IWG please review this Q&A in the light of experience in Europe? As part of the Q&A the following statement has been made “For the time being, other regions are able to accept appropriate use of node extensions in compliance with the eCTD specification (i.e. their use is discouraged unless there is no other feasible means to submit the information). The IWG will review this situation.” Experience in Europe is that routinely the node extension is being used, typically at the lowest level to differentiate between studies and so organize the files per study. Other examples are used higher up the backbone, wherever some differentiation is required that is not supported by attributes. No problems appear to be occurring and it would	Q&A No. 28 has been supplemented.	Approved	

820	GSK Canada	FDA	Specification v3.2 and regional specifications	In a subsequent submission, can the operation attribute 'new' be used against a document at a specific position in the backbone where there has already been a document in the previous submission? The vendor of an eCTD builder product has interpreted the spec that at no point in the lifecycle of the eCTD can there be submission of a document with the same name/title included where the operation attribute is assigned as new in the subsequent submission. An example would be where a variation/amendment contains a 'cover letter'. This is always related to the specific filing. 'New' is the attribute that should be used. 'Replace' or 'delete' are not relevant and 'append' is not appropriate to use since it is not necessary to refer to the previous as there may be no relationship intended. There are other examples where this issue can arise within Modules 2-5, for example in Module 2 where a QOS may be totally new and not rely upon		Approved for Q&A	No. 34
830	Liquent	PhRMA	Each Region's implementation guidance	Willingness of regions to accept eCTD only Which countries will accept eCTD only as official submission of archive? And under what conditions? Are there any non-ICH countries you are aware of	Regional authorities have communication on these questions - please refer to those	Rejected	

840	Liquent	PhRMA	Specification v3.2	<p>Versions of PDF files</p> <p>Will there be a mandate regarding the different versions of Acrobat documents to be accepted and/or expectations of backwards compatibility, while acknowledging that only recent versions that may be purchased? The latest Guidance document on the FDA site indicates PDF 1.4, and while Acrobat Distiller may be set to create lower version PDFs, once manipulated in a later version of Acrobat (which is often necessary to add hyperlinks, bookmarks, etc.) the file contains that</p>	see answer to Change request 00790	Rejected	
850	Liquent	PhRMA	Specification v3.2	<p>At the DIA EDM Conference someone asked about hyperlinks and submission lifecycles. For documents that the sponsor knows will be updated at a later date (e.g. as part of the 120-day safety update), the FDA said it was fine to not provide hyperlinks in the initial application; rather, you should provide a physical citation so that the reviewer can get there via the backbone. Is that approach acceptable in all regions?</p>	<p>This is a business related question, which cannot be answered by the eCTD IWG. Consult regional authorities on a case by case basis.</p>	Rejected	
860	Liquent	PhRMA	Specification v3.2	<p>Can you provide any best practice recommendations around using the append operation; is there an expectation that the content being appended will include contextual clues as to the portion of the original</p>	<p>This is a business related question, which cannot be answered by the eCTD IWG. Consult regional authorities on a case by case basis.</p>	Rejected	

870	Liquent	PhRMA	EU Regional specifications	With the issuance of v1.0 of the EU application form in XML, is there a timeframe when it will be accepted and/or mandated? Can you provide details as to how it and supportive files should be included in an eCTD (supportive files with the application form XML file or in the main util directory, etc.)?	EU regional question	Rejected	
880	Liquent	PhRMA	EU Notice to Applicants	Has any further discussion occurred regarding the handling of eCTD lifecycles in Mutual Recognition Procedures? It has been suggested that eCTD lifecycles may be 'branched' to help support multiple submissions to different concerned member states. Will further guidance clarify this soon?	EU regional question	Rejected	
890	Liquent	PhRMA	Specification v3.2	Can you provide further clarification on the related sequence element? Should it only contain references to sequences which are included in modified-file paths, or any sequence to which information being newly submitted may		Approved for Q&A	No. 35
900	Liquent	PhRMA		What is the training and education plan for agencies in Europe to aid them in understanding the implications of the lifecycle opportunities and challenges of eCTD?		Rejected	

910	Liquent	PhRMA	Specification v3.2	Are there any recommendations regarding the length of a document and the need for it to have its own internal table of contents? Are bookmarks representative of the document structure an acceptable substitute to a	Refer to page 7-3 of the Specification 3.2.	Rejected	
920	Liquent	PhRMA	US and EU Regional specifications	With the SPL and PIM initiatives, are there plans to issue specific guidance as to how to include these documents and their supportive files in an eCTD as well as address the lifecycle considerations?	Refer to regional guidances on Module 1	Rejected	
930	Liquent	PhRMA	eCTD DTD	Is it expected that the ID attribute for non-leaf elements will be used and are there lifecycle implications to using it?	An example would be helpful to understand this question.	Rejected	
940	Liquent	PhRMA	Specification v3.2	Is there a (technical or practical) limit to the number of characters used for the leaf ID? Would a GUID be considered appropriate for this value?	Reference to W3C standard?	Approved for specification change	
950	Liquent	PhRMA	Specification v3.2	If a document is appended multiple times – sequence 0001, 0002, and 0003 all contain a leaf with an operation=”append” and modify a leaf submitted in 0000, is there a point at which this becomes unwieldy from a review perspective? Is there an expectation that at some point, it makes more sense to replace the file submitted in 0000 with the sum-total that comprises the current document as a	This is a business related question, which cannot be answered by the eCTD IWG.	Rejected	

960	Liquent	PhRMA	eCTD DTD and Written Specification	How are the link-text and xref elements expected to be used in the eCTD? So far, we have not found application for them and would like to know where	There is no planned use for them today	Approved for specification change	
970	Liquent	PhRMA	Specification v3.2 and regional specifications	The November 2004 Q&A includes questions regarding the use of node-extensions (#28, Change Request 00560) and we understand from our customers that node-extensions are necessary in the EU, but they are specifically discouraged in the v3.2 Specification. Has further thought been given regarding the expectation of their	Duplicate change request, see 00810	Rejected	
980	Liquent	PhRMA	Specification v3.2	Are there any plans to update the ICH and/or regional Paper CTD specification(s) to further facilitate parallel submission of eCTD and paper while paper is still required in some regions (as in the EMEA v0.3 guidance document <i>Practical guidance for the paper submission of regulatory information in support of a marketing authorisation application when using the Electronic Common Technical Document ("eCTD") as the source</i> Link to ICH Q3B(R2) 2006)	Refer to regional guidances	Out of scope	
990	Liquent	PhRMA	Specification v3.2	Are there other sections of the eCTD in Modules 2-5 or any region's Module 1 that are being considered for XML/structured content as opposed to	For structured XML files refer to regional guidance. For use of XML in place of PDF refer to change request No. 00709	Out of scope	
1000	Liquent	PhRMA	Specification v3.2	Has any further discussion occurred to address the lifecycle linking issues of preventing stale links without requiring the resubmission of content?	see change request 00320	Deferred	

1010	Liquent	PhRMA	The eCTD Backbone File Specification for Study Tagging Files v2.6, November 2004	The v2.6 STF specification does not mention content-blocks, but they are still in the DTD; is there an expectation that these will be used, and if so, can examples be provided?	Refer to US regional guidance	Out of scope	
1020	Liquent	PhRMA	Specification v3.2	There is a zip file for v2.6 of STF on the ICH site, but the FDA site still has v1.1. Assuming the 2.6 version is the correct version to be used, if using the cumulative approach, and given how the format of the xlink:href changed from a folder/file path to the indirect reference of the backbone, and the change to the usage intent of the property element, if I have previously submitted STFs according to the 1.1 specification, should the new STF remove the property elements from the old doc-content elements and update the format of the xlink:href attributes? If the Accumulative approach is taken, do previously submitted STFs need to be replaced to reflect the current usage?	Refer to US regional guidance	Out of scope	
1030	Liquent	PhRMA	eCTD DTD	Are there any plans to use the leaf attributes of role, actuate, and/or show, or to remove them from the specification if they are not planned to	There is no planned use for them today.	Approved for specification change	

1040	Liquent	PhRMA	Guidance for Industry – Submitting Marketing Applications According to ICH-CTD Format	Is there an expectation that companies will continue to submit hybrids (eNDA/eBLA with CTD content) for a specific timeframe? Is there an expectation that any hybrid requirements will eventually be included in eCTD? Can FDA tell us how many hybrids they've received vs.		Out of scope	
1050	Liquent	PhRMA	US Module 1 v1.1 March 2004	Can you provide further clarification on the related sequence element? Should it only contain references to sequences which are included in modified-file paths, or any sequence to which information being newly submitted may	Duplicate change request, see 00890	Rejected	